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Title

The role of birth weight on the causal pathway to child and adolescent ADHD symptomatology: A population-based twin differences longitudinal design

SELF-ARCHIVING VERSION

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Abstract

Background: Available evidence points towards lower birth weight as a risk factor for the development of attention deficit/hyperactivity disorder (ADHD) symptoms. We probed the causal nature of this putative effect of birth weight on ADHD symptoms using the twin differences design, which accounts for genetic and shared environmental confounds.

Method: In a large population-based twin sample (N = 10,197 monozygotic, MZ, and dizygotic, DZ, pairs), parents, teachers or twins rated the twins' ADHD symptoms on rating scales at 9 assessment waves (2-16 years). We implemented the twin differences design, which accounts for shared environmental and genetic confounds, partially in DZ twins and totally in MZ twins. We tested whether: (i) the lighter-born twins had elevated ADHD symptoms compared to the heavier-born twins, by regressing within-pair differences in ADHD symptoms on within-pair differences in birth weight, separately in DZ and MZ twins; (ii) if the within-twin effect was moderated by sex, birth weight and gestational age; (iii) this effect changed with age using adapted latent growth curve models; and (iv) results differed for inattention and hyperactivity/impulsivity. **Results**: Birth weight significantly predicted ADHD symptoms from early childhood to late adolescence. The lighter-born twin had more ADHD symptoms than the heavier-born co-twin, in both MZ and DZ twins, across assessment waves and raters. The most stringent estimates – i.e. MZ estimates – indicated a plausible causal effect of lower birth weight on increased risk for ADHD symptomatology. Although significant at all ages, the magnitude of the effect of birth weight decreased significantly across time for hyperactivity/impulsivity, but not for inattention. Estimates for inattention were significantly larger than for hyperactivity/impulsivity at each time point, implying stronger effects of birth weight on inattention.

Conclusion: Our findings provide stringent evidence for environmental effects of lower birth weight on the causal pathway to elevated ADHD symptoms. Effects of birth weight persist across a 14-year period from childhood into late adolescence.

Keywords: ADHD, inattention, hyperactivity/impulsivity, birth weight, twin differences

Introduction

Birth weight is an index of fetal growth and a summary marker of the prenatal environment (Schlotz & Phillips, 2009). Lower birth weight is associated with a range of adverse mental health and behavioural outcomes, such as lower intelligence quotient (IQ; e.g. Breslau, 1995), autistic-like features (e.g. Ronald, Happé, Dworzynski, Bolton, & Plomin, 2010), conduct problems (e.g. Wiles et al., 2006) and attention-deficit/hyperactivity disorder (ADHD; e.g. Schlotz, Jones, Godfrey, & Phillips, 2008). The adverse outcomes associated with lower birth weight can be viewed in light of the developmental origins of health and disease (DOHaD) hypothesis(Barker, 1997, 2007). According to the DOHaD hypothesis, changes in prenatal environment during sensitive periods of organ development can result in long-term structural or physiological alterations, which subsequently increase the risk of diseases such as psychiatric disorders later in life(Barker, 1997, 2007).

Numerous epidemiological studies have shown that lower birth weight is associated with ADHD symptoms (Botting, Powls, Cooke, & Marlow, 1997; Breslau et al., 1996; Mick, Biederman, Prince, Fischer, & Faraone, 2002; Nigg & Breslau, 2007). A recent meta-analysis of 88 studies reported a small (r = -.15) but robust association between birth weight and ADHD symptoms (Momany, Kamradt, & Nikolas, 2017). Despite substantial epidemiological evidence, the reported association between lower birth weight and ADHD symptoms may not reflect a direct causal relationship. In particular, most epidemiological studies used correlational designs, which may be confounded by genetic and shared environmental factors. Twin studies have demonstrated that both ADHD and birth weight are heritable (76% and 40-50%, respectively; Clausson, Lichtenstein, & Cnattingius, 2000; Faraone et al., 2005; Magnus, 1984). Although previous twin studies suggested no common genetic liability between these two traits, residual genetic confounding is still possible (Groen-Blokhuis, Middeldorp, Van Beijsterveldt, & Boomsma, 2011; Pettersson et al., 2015). Shared environmental factors, associated with both birth weight and ADHD, such as socio-economic status (Blumenshine, Egerter, Barclay, Cubbin, & Braveman, 2010; Foulon et al., 2015) and prenatal smoking (Galéra et al., 2011; Thapar et al., 2009) may also confound this association. To further probe the nature of the relationship between birth weight and ADHD symptoms, the twin differences design can be implemented by comparing one twin to his or her co-twin (McGue, Osler, & Christensen, 2010). Both dizygotic (DZ) and monozygotic (MZ) twins share common environmental influences (i.e. environmental factors that make twins more similar to each other). DZ twins share approximately 50% of their segregated genes, and MZ twins share a 100% of their segregated genes. The co-twin design capitalizes on these twin characteristics to control for shared environmental and genetic confounding, partially in DZ twins and fully in MZ twins. Therefore, findings from the twin differences design, especially from MZ twins, provide stringent estimates of the role of birth weight on the causal pathway to developing ADHD symptoms.

A number of twin differences studies in childhood have demonstrated that lighter-born twins have elevated ADHD symptoms compared to heavier-born twins, suggesting that lower birth weight contributes to higher ADHD symptoms (Asbury, Dunn, & Plomin, 2006; Ficks, Lahey, & Waldman, 2013; Groen-Blokhuis et al., 2011; Hultman et al., 2007; Lehn et al., 2007; Pettersson et al., 2015). However, these studies were limited in several key ways. First, no twin differences study used longitudinal methods to examine whether the effect of birth weight on ADHD symptoms persisted in the long-term (i.e. from childhood to adolescence). The DOHaD hypothesis implies that the effect of birth weight on ADHD should persist in the long-term (Barker, 1997, 2007). However, the effects of birth weight on adverse developmental outcomes may attenuate with age. For example, catch-up growth appeared to alter the effects of lower birth weight on general cognitive and psychological performance in males (Lundgren, Cnattingius, Jonsson, & Tuvemo, 2001), although this was not observed for attention problems (Groen-Blokhuis et al. 2011).. To date, there is no twin differences study examining whether the effect of birth weight persists from childhood to later stages of life.

A second key limitation is that no previous twin differences study formally tested whether birth weight may differentially influence the development of the two ADHD symptom dimensions, i.e. inattention and hyperactivity/impulsivity. A singleton study showed that adolescents with low birth weight had significantly higher inattention when compared to controls but no difference in hyperactivity was detected (Indredavik et al., 2004). This effect might persist until young adulthood, as another singleton study found that 20-year-old adults born with very low birth weight had more inattention problems but not hyperactivity problems compared to controls (Hack et al., 2004). In their twin differences study, Pettersson et al. (2015) suggested that lower birth weight affects both ADHD symptom dimensions in childhood, but whether the magnitude of this effect differs significantly across both dimensions remains untested in a twin differences design. Also, most of the twin differences studies only used parents' ratings to assess ADHD symptoms (Ficks et al., 2013; Groen-Blokhuis et al., 2011; Hultman et al., 2007; Pettersson et al., 2015). This is potentially problematic as parental reports are prone to contrast effect, that is parents tend to highlight differences between twins, in particular for DZ twins (Thapar, Hervas, & McGuffin, 1995).

Lastly, a recent meta-analysis systematically investigated moderators of the association between birth weight and ADHD (Momany et al., 2017). In the current study, we tested whether the size of this association differed according to sex, gestational age, and whether it differed for low birth weight (< 2,500g) versus normal birth weight participants. Although the meta-analysis reported non-significant findings for these three moderators, we aimed to confirm this finding within the twin difference design. This is the first large population-based twin differences study to examine the differential effects of birth weight on both ADHD symptom dimensions, assessed by multiple informants across a 14-year period. We tested whether the relationship between birth weight and ADHD symptoms:

(i) remained after controlling for genetic and shared environmental confounds and was moderated by sex;

(ii) persisted from childhood to adolescence; and

(iii) whether differential effects of birth weight on the two ADHD symptom dimensions could be detected.

Methods

Participants

Participants were drawn from the Twins Early Development Study (TEDS), a large longitudinal study of twins born in England and Wales between 1994 and 1996, which is representative of the UK population as shown in Table S1 (Haworth, Davis, & Plomin, 2013). Their zygosity was determined using a parent-rated instrument, which is 95% as accurate as DNA markers (Price et al., 2000). Analyses were conducted after excluding twin pairs with extreme perinatal conditions, severe medical conditions, uncertain zygosity, unknown sex, incomplete birth weight record and no data on ADHD symptoms. The final sample included 10,197 twin pairs (6,698 DZ pairs, 3,499 MZ pairs, 51.2% females). The number of twin pairs included in each analysis ranged from 3,176 pairs to 7,119 pairs (See Table 1), depending on age, ADHD scale and informants. The present study included nine waves of assessments when twins were between 2 and 16 years old. Written informed consent was obtained from all participating families. This study was approved by the Institute of Psychiatry, Kings College London, Ethics Committee.

Measures

Birth weight. During first contact, parents reported each twin's birth weight in pounds or kilograms, which were then converted into grams for analyses. Twins' median age was 1.6 years when birth weight data was collected.

ADHD symptoms. ADHD symptoms were assessed using age-appropriate parent-reported questionnaires, which are Behar's Preschool Behaviour Questionnaire (BPBQ; Behar & Stringfield, 1974) at ages 2, 3 and 4 years, the hyperactivity-inattention subscale of Strength and Difficulties Questionnaire (SDQ; Goodman, 1997) at ages 4, 7, 9, 12, and 16 years, and the DSM-IV based ADHD subscale of the Conners' Parent Rating Scale – Revised (CPRS-R; Conners, 2001) at ages 8, 12, 14, and 16 years. There were also teacher-reported questionnaires (SDQ at ages 7, 9, and 12 years) and self-reported questionnaires (SDQ at ages 9, 12 and 16 years). All measures are standard ADHD scales with adequate psychometric properties (See footnote of Table S2 for additional details on individual measures).

Statistical Analyses

All analyses were conducted using R Version 3.3.1 (R Core Team, 2016) and its Structural Equation Modelling package Lavaan Version 0.5-22 (Rosseel, 2012).

Twin differences analyses

Using the twin differences design, we tested whether birth weight predicted ADHD symptoms at each wave of assessment. In order to examine the whole spectrum of birth weight differences, twin pairs were included irrespective of within-twin pair differences in birth weight. Prior to analysis for each ADHD scale, twins with missing ADHD data on that particular measure were excluded and all variables were standardised.

Response rates were systematically lower for teacher and self-reports than for parental reports at the same data collection point. We therefore created two SDQ scores across ages to maximize sample size (i.e. teacher-rated SDQ at ages 7, 9 and 12 years and self-report SDQ at ages 9, 12 and 16 years). We did not include teacher and self-reported measures available at only one data collection point.

Analysed measures and their corresponding number of twin pairs are listed in Table 1.

Three types of estimates were obtained: (1) the unadjusted phenotypic estimates from the whole twin sample, (2) the estimates from twin differences in DZ same-sex twins (DZ estimates) and (3) the estimates from twin differences in MZ twins (MZ estimates).

To obtain unadjusted phenotypic estimates, non-independence of data within twin pairs was accounted for by allowing within-twin correlations (Carlin, Gurrin, Sterne, Morley, & Dwyer, 2005). DZ and MZ estimates were obtained by conducting Ordinary Least Square (OLS) regressions through origin, regressing within-twin differences in ADHD symptoms on within-twin differences in birth weight (Carlin et al., 2005). DZ and MZ estimates are standardized beta coefficients from these regressions, obtained separately in same-sex DZ pairs and MZ pairs.

To account for non-normality and non-independence, robust 95% confidence intervals (CI) were obtained using bootstrapping (10, 000 repetitions) for all three types of estimates. The moderating effect of sex on these estimates was tested using the same method employed to test the differential effect of birth weight on the two symptom dimensions of ADHD, as described in a later section.

Unadjusted phenotypic estimates are bivariate correlations between birth weight and ADHD symptoms without controlling for any potential genetic and shared environmental confounds. DZ twins share about 50% of their segregated genes and 100% of their shared environment. Consequently, DZ estimates are more stringent than unadjusted phenotypic estimates because all shared-environmental confounds and part of genetic confounds are accounted for. Since MZ twins share 100% of their segregated genes and 100% of their shared environment, MZ estimates are even more

robustly adjusted than DZ estimates, accounting fully for both genetic and shared environmental influences.

Modelling developmental effects

Latent growth curve modelling was used to investigate if the change in MZ estimates was significant across development. In each MZ twin pair, one twin was assigned as "heavier twin" and another as "lighter twin" accordingly. 171 MZ twin pairs with equal birth weight were excluded. The development of ADHD symptoms in lighter versus heavier twins was then modelled from age 8 to age 16 years, using the CPRS-R , which provides a comprehensive assessment of both ADHD dimensions based on the DSM IV, and has been used extensively as a rating scale for ADHD diagnosis (Chang, Wang, & Tsai, 2016). Analyses were conducted for the total ADHD symptoms and repeated for the two symptom dimensions. The growth model included linear and quadratic components to account for non-linear change. Missing data was handled using full information maximum likelihood (FIML) method.

To examine the developmental trend, we investigated whether:

i. the differences in ADHD symptoms between "lighter" and "heavier" twins were significant at age 8 and 16 years (i.e. difference in means in both groups, tested at both ages); and

ii. whether this difference in means between "lighter" and "heavier" twins was significantly larger at age 8 compared to age 16 years (difference observed at age 8 years minus difference at age 16 years). Computed estimates for (i) and (ii) were bootstrapped 10,000 times to obtain 95% confidence intervals.

Differential effects on symptom dimensions

To test whether the MZ estimates significantly differed depending on ADHD symptom dimensions, further analyses were carried out in MZ twins using the CPRS-R, which has nine items for each symptom dimension. Two models were fitted for each of the symptom dimensions assessed at different ages. In the first model, the MZ estimates for both symptom dimensions were constrained to be the same. The second model did not include equality constraints, thereby allowing both MZ estimates to be different. The difference in goodness of fit was then tested using the Satorra-Bentler Chi-square test. A significant test indicates that the effect of birth weight differs for the two dimensions. The same method was also used to test the effect of sex as a moderator for MZ estimates (See Table S4).

Results

Twin differences analyses

Descriptive sample statistics regarding mean birth weight, number of twins and gender proportion for each ADHD measure are shown in Table S2. The mean gestational age was 36.47 weeks for the whole sample and 36.21 weeks for MZ twins.

As shown in Table 1, most phenotypic estimates were significant during childhood (e.g. at age 4 years, the estimate for parent-rated SDQ was β = -.075, 95% CI: -.091, -.058), but became nonsignificant in adolescence (e.g. at age 16 years, the estimate for parent-rated SDQ was -.024, 95% CIs: -.046, .000). In contrast, despite being the most stringent type of estimates, all MZ estimates were significant from early childhood to adolescence with small effect sizes ranging from β = -.007 to β = -.237. These effect sizes were not moderated by sex, birth weight and gestational age (see Table S4, S5 and S6). Complementary analyses showed that a difference in 1 kilogram in birth weight corresponded to, e.g. a difference of 0.42 symptom for inattention and 0.17 symptom for hyperactivity/impulsivity at age 8 years (see Table S8 for additional details).

[Insert Table 1 here]

Modelling Developmental Effects

The change in ADHD symptoms for heavier versus lighter-born MZ twins is shown in *Figure 1* for total ADHD symptoms (See *Figure S1* for inattention and *Figure S2* for hyperactivity/impulsivity).

[Insert *Figure 1* here]

At age 8 years, there was a significant difference of ADHD symptoms between heavier and lighter-born twins. Lighter-born twins tended to have higher total ADHD, inattention and hyperactivity/impulsivity symptoms (see Table 2). At age 16 years, lighter-born twins tended to have higher total ADHD and inattention symptoms. Differences between heavier and lighter-born twins decreased between age 8 and age 16 years, consistent with a lessening effect of birth weight over time. Decrease was observed for total and hyperactivity/impulsivity symptoms but failed to reach significance for inattention symptoms (see Table 2). The growth parameters are presented in Table S3.

[Insert Table 2 here]

Differential effect on symptom dimensions

Figure 2 shows that MZ estimates for inattention symptoms appear larger in magnitude than for hyperactivity/impulsivity. Formal Satorra-Bentler tests revealed that the unconstrained models fit the data better than the constrained models from age 8 years to 16 years, suggesting that the stronger effect of birth weight on inattention compared to hyperactivity/impulsivity was significant and enduring (see Table 3).

[Insert *Figure 2* here]

[Insert Table 3 here]

Discussion

In the current twin differences study, we report three main findings. First, the epidemiological association observed between birth weight and ADHD symptomatology was confirmed in stringent twin differences analyses using DZ and MZ twins to control for genetic and shared environmental confounding. This points towards a plausible role of birth weight on the causal pathway leading to the development of ADHD symptoms. Second, birth weight effect on ADHD symptoms persisted from childhood to adolescence. Third, this effect was stronger and more persistent for inattention compared to hyperactivity/impulsivity.

The present findings confirm previous twin studies, such as Pettersson et al. (2015) as the effects of birth weight remained significant even in MZ analyses, which control for all shared environmental and genetic confounding. Our findings add to the literature in that we used a large population-based sample of twins, with consistent findings across multiple ADHD scales and multiple informants. In addition, using a twin differences design, we found that the effect of birth weight was not moderated by sex, which confirms findings from a recent meta-analysis (Momany et al., 2017). The small MZ estimates found in this study are the rule rather than exception in MZ differences analyses. This may reflect that the environmental architecture underlying ADHD is just as complex as their genetic architecture, which is assumed to involve multiple probabilistic genes of miniscule effects (Donnelly, 2008). A recent meta-analysis of 88 studies reported a small overall correlation between birth weight and ADHD symptoms (r = - 0.15), with a correlation of r = -0.09 when considering population-based studies only (Momany, Kamradt, & Nikolas, 2017). Our findings are consistent with these effect sizes.

Intriguingly, MZ twin differences estimates were larger than phenotypic correlations between birth weight and ADHD symptoms. This pattern of findings replicates what was observed in a previous twin differences study of birth weight and ADHD (Pettersson et al., 2015), suggesting that our finding is not sample specific. Because the twin differences design stringently controls for genetic and shared environmental confounds, MZ estimates are typically lower than phenotypic estimates. Interestingly, the aforementioned meta-analysis reported a slightly larger effect size (r = -0.18) in covariate-adjusted analyses compared to unadjusted analyses (r = -0.15, Momany, Kamradt, & Nikolas, 2017). This is consistent with a suppression effect, i.e. confounders hide the true effect of birth weight as a risk factor for ADHD symptoms. As the twin differences design accounts for unobserved confounders, the level of adjustment is more stringent than in classical epidemiological designs. It may thus not be surprising that the differences between phenotypic and MZ estimates appear larger in our study than the difference between adjusted and unadjusted estimates in the meta-analysis.

Longitudinal findings in the current study add to current knowledge that a) the effects of low birth weight on ADHD symptoms were persistent from age 2 to age 16 years; b) although persistent, effects of birth weight decreased with age for hyperactivity/impulsivity.. These findings

support the DoHAD hypothesis(Barker, 1997, 2007) , in which prenatal environment constitutes a long-term risk. Prenatal ischemia hypoxia (i.e. insufficient nutrients and oxygen supply in utero) is a primary pathway to lower birth weight, and a review found that it also produces lasting changes in neurodevelopmental functioning, which increases risk for ADHD (Smith, Schmidt-Kastner, McGeary, Kaczorowski, & Knopik, 2016). In addition, non-twin studies showed that the birth weight-ADHD association is mediated by impaired brain functions, supporting that lower birth weight interferes with cerebral development, leading in turn to ADHD development (Hatch, Healey, & Halperin, 2014). Future twin studies with brain data may be able to pinpoint which cerebral regions underlie the effect of birth weight on ADHD symptoms.

Despite still being significant at age 16 years, effects of birth weight on total ADHD symptoms and hyperactivity/impulsivity decreased. Therefore, while supporting the DoHAD hypothesis, our study provides additional support for a developmental compensation effect whereby prenatal risk is partially compensated over time. Interestingly, age was not found to be a moderator of the effect of birth weight on ADHD symptoms in a meta-analysis (Momany et al., 2017). Directly modelling the longitudinal effects of birth weight in a twin differences design may have allowed us to better detect this change of effect across ages. Alternatively, this finding may be sample specific and would warrant replication.

The stronger phenotypic association between birth weight and inattention than hyperactivity/impulsivity has been reported in previous studies (Hack et al., 2004; Indredavik et al., 2004) and was confirmed here using the twin differences design. We found that the persisting effect of birth weight on inattention symptoms persisted into adolescence, whereas the effect on hyperactivity/impulsivity symptoms decreased, which further supported the differential effect of birth weight on the two symptom dimensions. Importantly, although not significant, the developmental trend of findings was similar for inattention and hyperactivity/impulsivity. At age 16 years, the difference in hyperactivity/impulsivity between lighter and heavier twins was 65% smaller than at 7 years. For inattention, this difference was 27%, not significant, and should be tested in larger samples.

Limitations

Our findings point towards the importance of birth weight –an important marker for fetal growth– in the aetiology of long-term ADHD symptoms. However, birth weight is a complex risk factor, and further research is needed to identify which aspects of fetal growth might explain the findings (e.g. by identifying restricted development in specific brain areas). In addition, other prenatal unmeasured non-shared environmental factors associated with fetal growth apart from birth weight, such as positioning in the womb, placentation, or differences in nutritional availability could also explain the findings (Plomin, DeFries, Knopik, & Neiderhiser, 2013). Post-natal differences within twin pairs may be due to different birth weights (e.g. additional intervention for the lighter twin). Such post-natal differences may mediate

the effect of birth weight on ADHD symptoms, which warrants further investigation. Another limitation is that the current study included retrospective parental reports of birth weight, which may be affected by recall bias. However, retrospective parental reports of birth weight have been shown to be reliable up to 30 years post-birth (Catov et al., 2006; Lumey, Stein, & Ravelli, 1994). Furthermore, a meta-analysis reported no difference in the size of association between birth weight and ADHD, when using medical records or retrospective parental reports for birth weight (Momany et al., 2017).

Conclusion

Restricted fetal development, as indexed by reduced birth weight, may play a role in non-shared environmental pathways leading to the development of ADHD symptomatology. Whereas this effect was found to decrease across time for total ADHD symptoms and hyperactivity/impulsivity, the decrease failed to reach significance for inattention. In addition, birth weight was found to influence inattention more strongly than hyperactivity/impulsivity across childhood and adolescence.

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Table 1.

Phenotypic and MZ twin difference estimates of the relationship between birth weight and ADHD symptoms.

Age	Measure	Phenotypic estimate, β (95% CI)	MZ estimate, β (95% CI)	Total N (MZ)
Parents' ratings				
2	**BPBQ**	**-.086 (-.106, -.065)**	**-.126 (-.178, -.074)**	5,562 (1,910)
3	**BPBQ**	**-.078 (-.097, -.057)**	**-.190 (-.241, -.143)**	5,423 (1,876)
4	**BPBQ**	**-.073 (-.090, -.056)**	**-.193 (-.242, -.145)**	7,119 (2,445)
4	**SDQ**	**-.075 (-.091, -.058)**	**-.193 (-.245, -.139)**	7,113 (2,445)
7	**SDQ**	**-.066 (-.083, -.048)**	**-.237 (-.290, -.184)**	7,011 (2,524)
8	**CPRS total**	**-.052 (-.071, -.032)**	**-.115 (-.153, -.078)**	6,112 (2,177)
8	**CPRS H/I**	**-.049 (-.068, -.029)**	**-.064 (-.096, -.031)**	6,110 (2,177)
8	**CPRS IA**	**-.046 (-.065, -.026)**	**-.146 (-.190, -.101)**	6,109 (2,177)
9	**SDQ**	**-.074 (-.101, -.048)**	**-.169 (-.221, -.114)**	3,176 (1,176)
12	**SDQ**	**-.057 (-.077, -.036)**	**-.157 (-.203, -.114)**	5,458 (1,992)
12	**CPRS total**	**-.044 (-.063, -.023)**	**-.095 (-.133, -.056)**	5,463 (1,987)
12	**CPRS H/I**	**-.033 (-.053, -.013)**	**-.043 (-.074, -.012)**	5,461 (1,987)
12	**CPRS IA**	**-.045 (-.065, -.024)**	**-.122 (-.173, -.077)**	5,463 (1,986)
14	**CPRS total**	**-.030 (-.056, -.003)**	**-.090 (-.140, -.053)**	3,194 (1,232)
14	**CPRS H/I**	-.026 (-.051, .000)	**-.047 (-.084, -.010)**	3,189 (1,231)
14	**CPRS IA**	**-.027 (-.055, -.001)**	**-.108 (-.174, -.059)**	3,193 (1,232)
16	**SDQ**	-.024 (-.046, .000)	**-.112 (-.163, -.057)**	4,699 (1,705)
16	**CPRS total**	-.021	**-.097**	4,706

		(-.044, .001)	**(-.141, -.050)**	(1,708)
16	**CPRS H/I**	**-.033**	**-.038**	4,704
		(-.056, -.011)	**(-.082, -.001)**	(1,707)
16	**CPRS IA**	-.006	**-.120**	4,705
		(-.029, .017)	**(-.173, -.065)**	(1,708)
Teachers' ratings				
-	**Mean SDQ**	-.010	**-.070**	7,049
		(-.028, .009)	**(-.107, -.028)**	(2,523)
Self-report				
-	**Mean SDQ**	.0163	**-.121**	6,783
		(-.002, .034)	**(-.177, -.065)**	(2,429)

Note. N = number of twins for each analysis. DZSS = DZ same-sex twins. H/I = Hyperactivity/impulsivity. IA= inattention. BPBQ = Behar's Preschool Behaviour Questionnaire. SDQ = Strength and Difficulties Questionnaire. CPRS-R = Conners' Parent Rating Scale - Revised. Estimates in bold are significant. Teachers' and self-report ratings were obtained based on the average ratings across different ages. Note that the CI of MZ estimate for CPRS-R H/I (16 years) is very close to zero and hence should be treated with caution.

Table 2.

Latent growth curve modelling parameters for total ADHD, inattention and hyperactivity/impulsivity symptoms.

	Predicted estimates (95% CI)		
	Heavier twins	Lighter twins	Within-twin Difference of ADHD symptoms
Total ADHD symptoms			
Mean at age 8 years	10.80 (10.44, 11.18)	11.50 (11.11, 11.88)	**-.70 (-.91, -.48)**
Mean at age 16 years	6.36 (6.04, 6.70)	6.75 (6.43, 7.10)	**-.40 (-.62, -.15)**
Difference of means (8 vs 16 years)	-	-	**-.30 (-.59, -.01)**
Inattention symptoms			
Mean at age 8 years	5.00 (4.81, 5.21)	5.44 (5.23, 5.65)	**-.44 (-.57, -.30)**
Mean at age 16 years	3.78 (3.57, 3.99)	4.09 (3.88, 4.31)	**-.31 (-.48, -.15)**
Difference of means (8 vs 16 years)	-	-	-.12 (-.31, .07)
Hyperactivity/ impulsivity symptoms			
Mean at age 8 years	5.79 (5.59, 6.00)	6.05 (5.84, 6.27)	**-.26 (-.36, -.15)**
Mean at age 16 years	2.57 (2.41, 2.73)	2.65 (2.49, 2.81)	-.08 (-.19, .03)
Difference of means (8 vs 16 years)	-	-	**-.17 (-.32, -.04)**

Note. Estimates in bold are significant. Heavier MZ twins had a mean birth weight of 2,592 grams, whereas lighter MZ twins had a mean birth weight of 2,283 grams

Table 3.

Satorra-Bentler test results of the differential effect of birth weight on ADHD symptom dimensions.

Age	Model	Df	χ2	χ2 (Df) difference	P-value
8	Unconstrained	2	1.60	17.32 (1)	p < .001***
	Constrained	3	24.14		
12	Unconstrained	2	.02	12.74 (1)	p < .001***
	Constrained	3	14.90		
14	Unconstrained	2	2.40	4.44 (1)	p = .035*
	Constrained	3	7.84		
16	Unconstrained	2	.69	8.84 (1)	p = .003**
	Constrained	3	12.86		

Note. Df=degrees of freedom. * p <.05; ** p <.01; *** p <.001

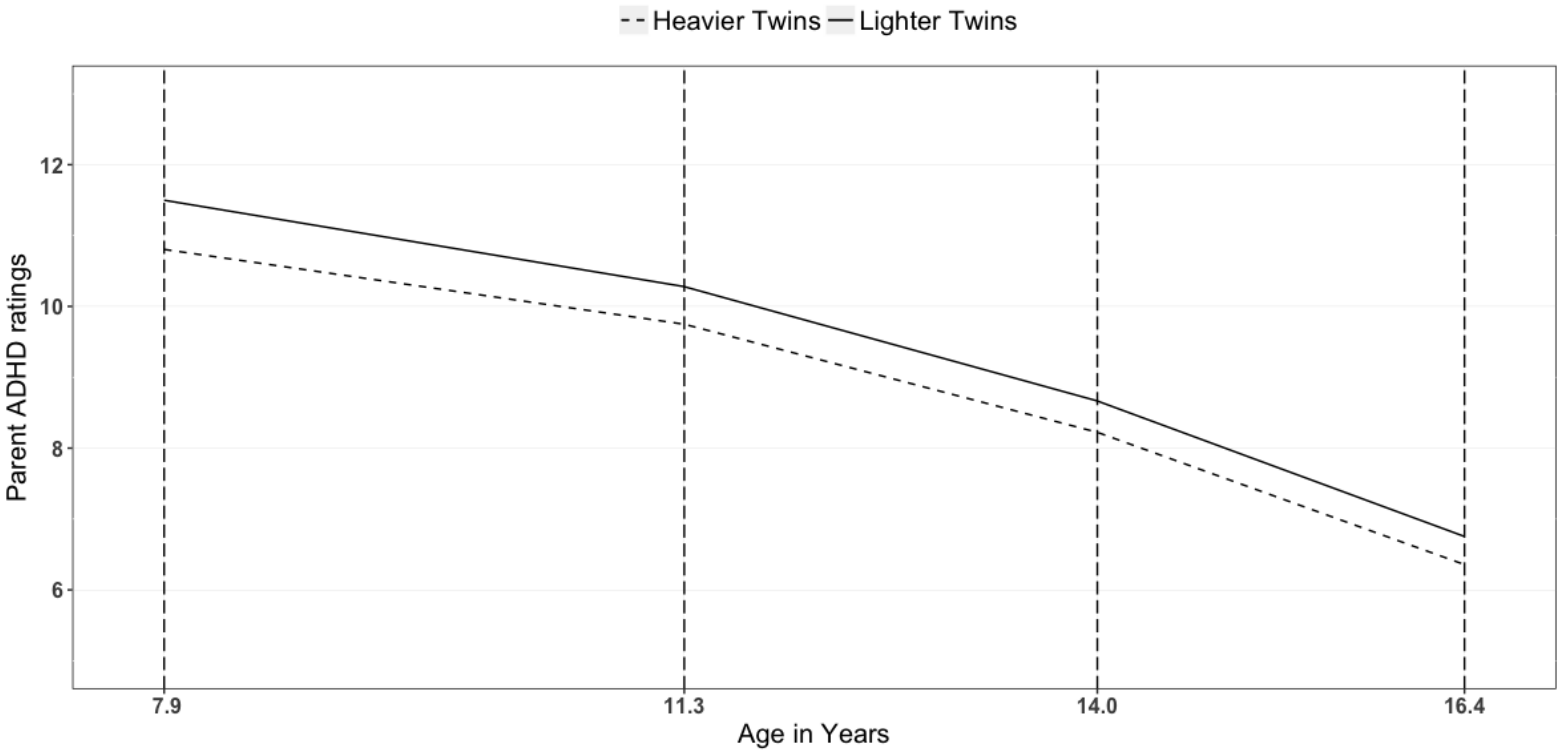

Figure 1: Predicted ADHD symptoms of MZ twins for CPRS-R from age 8 years to 16 years.

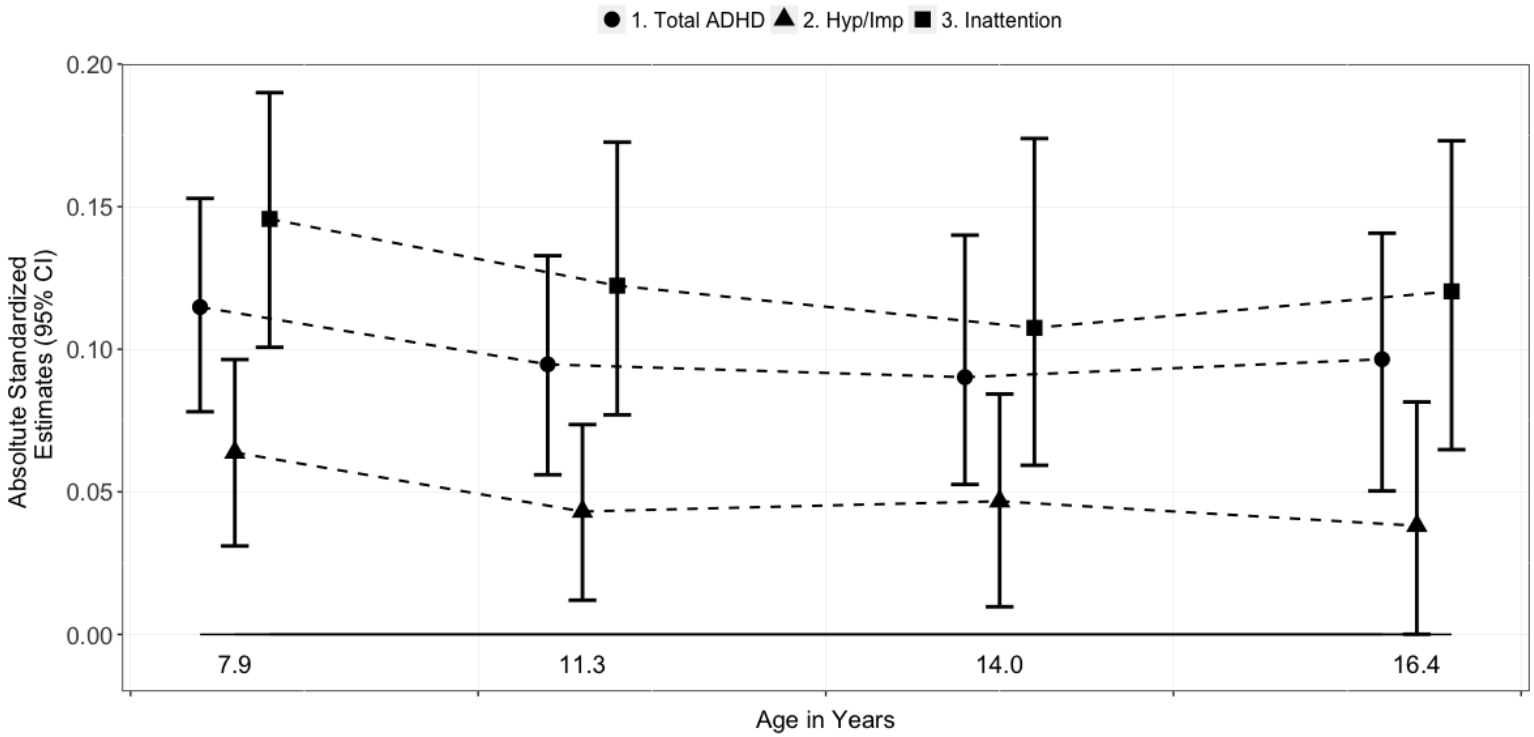

Figure 2: Absolute standardised MZ estimates with 95% CI for CPRS-R total ADHD, hyperactivity/impulsivity (Hyp/Imp) and inattention symptoms across ages 8, 12, 14 and 16 years. All estimates are absolute values (negatively signed estimates are presented in Table 1). The larger the estimates, the greater the effect of birth weight on ADHD symptoms.

Key points:

- Using a longitudinal twin differences design, we probed the causal nature of the observed association between birth weight and ADHD symptoms.
- Lower birth weight predicted higher ADHD symptoms over a 14-year period from childhood to adolescence, and this effect was not moderated by sex.
- Although still significant in adolescence, the size of the effect of birth weight decreased significantly for total ADHD and hyperactivity/impulsivity symptoms.
- A stronger and more persistent effect of birth weight was found for inattention compared to hyperactivity/impulsivity.
- Additional research to further dissect the mechanisms explaining this environmentally driven relationship between birth weight and ADHD symptoms are required.